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PATENT TRADEMARK OFFICE

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US) (ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/28972	8 December 1999	11 December 1998

TITLE OF INVENTION

USE OF ACETYLCHOLINESTERASE INHIBITORS ON THE MODULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

APPLICANT(S)

Bonnie DAVIS

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. §1.491 which states: "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1.494 and § 1.495."

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date November 27, 2001, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EV 011019365 US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

JENNIFER RASHKIN
(type or print name of person mailing paper)

Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

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*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

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WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[X]*	TOTAL CLAIMS	24 - 20 =	4	x $ 18.00 =	$72.00
	INDEPENDENT CLAIMS	3 - 3 =	0	x $ 84.00 =	
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $280.00				
BASIC FEE**	[X] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [X] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $710.00 [ ] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $740.00 [ ] has not been paid (37 CFR 1.492(a)(3)) ..... $1,040.00 [ ] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $890.00				$100.00
				Total of above Calculations	=$172.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Statement may also be filed. (note 37 CFR 1.9, 1.27, 1.28)				- $ 86.00
				Subtotal	
				Total National Fee	$86.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL				Total Fees enclosed	$86.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. [X] A check in the amount of $86.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [X] is not required, as the application was filed with the United States Receiving Office.
c. [ ] has been transmitted
i. [ ] by the International Bureau.
Date of mailing of the application (from form PCT/IB/308): _____.
ii. [ ] by applicant on _____.
Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [ ] is transmitted herewith.
b. [X] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
Date
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____.
   Date
c. [X] have not been transmitted as
   i. [X] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210): 4 APRIL 2000.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [ ] A copy of the international examination report (PCT/IPEA/409)
[ ] is transmitted herewith.
[X] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [ ] is/are transmitted herewith.
b. [X] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
    a. [ ] was previously submitted by applicant on _____. Date
    b. [ ] is submitted herewith, and such oath or declaration
        i. [ ] is attached to the application.
        ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
    c. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
    a. [ ] is transmitted herewith.
    b. [ ] has been transmitted by the International Bureau.
    Date of mailing (from form PCT/IB/308): _____.
    c. [X] is not required, as the application was searched by the United States International Searching Authority.
    d. [ ] will be transmitted promptly upon request.
    e. [ ] has been submitted by applicant on _____. Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
    a. [X] is transmitted herewith.
    Also transmitted herewith is/are:
    [X] Form PTO-1449 (PTO/SB/08A and 08B).
    [X] Copies of citations listed.
    b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
    c. [ ] was previously submitted by applicant on _____. Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [ ] Additional documents:
    a. [ ] Copy of request (PCT/RO/101)
    b. [ ] International Publication No. _____
        i. [ ] Specification, claims and drawing
        ii. [ ] Front page only
    c. [X] Preliminary amendment (37 C.F.R. § 1.121)
    d. [X] Other

    WRITTEN ASSERTION _____
    _____
    _____

15. [X] The above checked items are being transmitted
    a. [ ] before 30 months from any claimed priority date.
    b. [X] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on
    _____, namely:

    _____
    _____
    _____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425 .

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must

only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: *Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).*

NOTE: *37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.*

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 31053

JOHN RICHARDS
(type or print name of practitioner)

Tel. No.: (212)708-1915

LADAS & PARRY
P.O. Address

Customer No.: 00140

26 WEST 61ST STREET
NEW YORK, N.Y. 10023

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	BONNIE **DAVIS**
International Application No.	:	PCT/US99/28972
International Filing Date	:	8 DECEMBER 1999
Priority Date Claimed	:	11 DECEMBER 1998
For	:	USE OF ACETYLCHOLINESTERASE INHIBITORS ON THE MODULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS
Attorney Docket No.	:	U 013729-7

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Please amend the above identified application as follows:

IN THE CLAIMS

3. (Amended) A method as claimed in claim 1, wherein said condition is failure of ovulation.

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
*(When using Express Mail, the Express Mail label number is **mandatory**; Express Mail certification is optional.)*

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☐ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

37 C.F.R. 1.8(a)

☐ with sufficient postage as first class mail.

37 C.F.R. 1.10*

☒ as "Express Mail Post Office to Addressee" Mailing Label No. EV 011019365 US **(mandatory)**

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

Date: November 27, 2001

Signature
JENNIFER RASHKIN
(type or print name of person certifying)

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*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

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4. (Amended) A method as claimed in claim 1, wherein said defect is an unexplained infertility.

5. (Amended) A method as claimed in claim 1, wherein said condition is a luteal phase defect.

6. (Amended) A method as claimed in claim 1, wherein said defect is hypogonadotrophic hypogonadism.

7. (Amended) A method as claimed in claim 1, wherein said condition is aesthenozoospermia.

8. (Amended) A method as claimed in claim 1, wherein said condition is oligozoospermia.

9. (Amended) A method as claimed in claim 1, wherein said condition is delayed onset of puberty.

10. (Amended) A method as claimed in claim 1, wherein said condition is cryptorchidism.

11. (Amended) A method as claimed in claim 1, wherein said acetyl cholinesterase inhibitor is selected from the group consisting of donepezil, rivastigmine, galantamine, lycoramine and the analogs of galantamine and lycoramine.

12. (Amended) A method as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

13. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

14. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

18. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

19. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, Trifluoro methyl groups and halo groups.

20. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

21. (Amended) A method of treatment as claimed in claim 1, wherein said acetylcholinesterase inhibitor is galanthamine.

22. (Amended) A method of treatment as claimed in claim 1, wherein said

acetylcholinesterase inhibitor is rivastigmine.

23. (Amended) A medicine for treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis which comprises an effective amount of an acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours.

Respectfully submitted,

JOHN RICHARDS
LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO.31053(212)708-1905

MARKED-UP COPY

4. (Amended) A method as claimed in claim 1, [or claim 2] wherein said defect is an unexplained infertility.

5. (Amended) A method as claimed in claim 1, [or claim 2] wherein said condition is a luteal phase defect.

6. (Amended) A method as claimed in claim 1, [or claim 2] wherein said defect is hypogonadotrophic hypogonadism.

7. (Amended) A method as claimed in claim 1, [or claim 2] wherein said condition is aesthenozoospermia.

8. (Amended) A method as claimed in claim 1, [or claim 2] wherein said condition is oligozoospermia.

9. (Amended) A method as claimed in claim 1, [or claim 2] wherein said condition is delayed onset of puberty.

10. (Amended) A method as claimed in claim 1, [or claim 2] wherein said condition is cryptorchidism.

11. (Amended) A method as claimed in claim 1, [or claim 2] wherein said acetyl cholinesterase inhibitor is selected from the group consisting of donepezil, rivastigmine, galantamine, lycoramine and the analogs of galantamine and lycoramine.

12. (Amended) A method as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

13. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

14. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

18. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

19. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, Trifluoro methyl groups and halo groups.

20. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

21. (Amended) A method of treatment as claimed in claim 1, [or claim 2] wherein said acetylcholinesterase inhibitor is galanthamine.

22. (Amended) A method of treatment as claimed in claim 1, [or claim 2]

wherein said acetylcholinesterase inhibitor is rivastigmine.

23. (Amended) A medicine for [treatment] treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis which comprises an effective amount of an acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours.

USE OF ACETYLCHOLINESTERASE INHIBITORS ON THE MODULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Field of the Invention

The present invention relates to the use of centrally-acting cholinesterase inhibitors to modulate the hypothalamic-pituitary-gonadal axis by stimulating the secretion of gonadotropin releasing hormone. Such modulation finds use in, for example, stimulation of ovulation, in treatment of luteal phase defect, aesthenozoospermia, oligozoospermia, hypogonadotrophic hypogonadism and cryptorchidism and in induction of puberty.

Background of the Invention

The purpose of this invention is to influence the secretion of gonadotropin releasing hormone (GnRH - may be known as GRF, previously referred to as LHRH or LRF) using orally-active preparations influencing central cholinergic activity.

The addition of acetylcholine to anterior pituitary glands incubated with hypothalamic fragments results in luteinizing hormone (LH) release, which can be blocked by muscarinic blockade by atropine. Prostigmine, an acetylcholinesterase inhibitor, as well as acetylcholine, enhance LH release in this system. (Fiorindo RP and Martini L, Evidence for a cholinergic component in the neuroendocrine control of luteinizing hormone secretion. Neuroendocrinology 18:322-332, 1975). Follicle stimulating hormone (FSH) levels are increased by the addition of hypothalamic fragments to incubated anterior pituitary glands, with a further increase produced by acetylcholine, an effect antagonized by atropine. (Simonovic I, Motta M and Martini L, Acetylcholine and the release of follicle stimulating hormone releasing factor. Endocrinology 95:1371, 1974). As cholinergic agents have no direct effect on anterior pituitaries to stimulate LH or FSH release, they were presumed to release gonadotropin-releasing hormone (GnRH, formerly thought to be two hormones, luteinizing hormone releasing hormone, LHRH, and follicle stimulating hormone releasing hormone, FSHRH) from the hypothalamus. Since the advent of assays for GnRH, this fact has been directly demonstrated. (Richardson SB, Prasad JA, Hollander CS, Acetylcholine, melatonin, and potassium depolarization stimulate release of luteinizing

hormone-releasing hormone from rat hypothalamus *in vitro*. Proc Natl Acad Aci U S A 79(8):2686-9, 1982). In intact rats, injection of acetylcholine into the lateral ventricle stimulates LH release. This can be blocked with atropine or enhanced with prostigmine. Thus, cholinergic stimulation appears to cause GnRH release from the hypothalamus, apparently by a muscarinic mechanism.

Both muscarinic cholinergic blockade with atropine and nicotinic cholinergic stimulation appear to suppress gonadotropin release via hypothalamic mechanisms. Hemicastration in the female rat normally results in gonadotropin-mediated hypertrophy of the remaining ovary. This can be blocked by atropine implants into the anterior hypothalamus. (Monti JM, Sala MA, Otegui JE et al, Inhibition of ovarian compensatory hypertrophy by implants of atropine in the hypothalamus. Experientia 26:1263-1264, 1970). Similar implants blocked the post-orchidectomy rise in LH and FSH in male rats. No effect was seen of atropine implants into the pituitary, a finding consistent with the inability of acetylcholine to stimulate gonadotropin release from pituitary glands *in vitro*, as noted above. (Libertun C and McCann SM, Blockade of the postorchidectomy increase in gonadotropin by implants of atropine into the hypothalamus, Proc Soc Exp Biol Med 152:143-146, 1976). These data are consistent with the existence of a muscarinic cholinergic mechanism mediating GnRH release in the hypothalamus.

Conversely, nicotine administration suppresses LH secretion with consequent delay or inhibition of ovulation. (Blake CA, Parallelism and divergence in luteinizing and follicle stimulating hormone release in nicotine-treated rats. Proc Soc Exp Biol Med 145:716-720, 1974; Kanematsu S and Sawyer CH, Inhibition of the progesterone-advanced LH surge at proestrus. Proc Soc Exp Biol Med 143:1183-5, 1973; Blake CA, Scaramuzzi RJ, Norman RL, Kanematsu S and Sawyer CH, Nicotine delays the ovulatory surge of luteinizing hormone in the rat. Proc Soc Exp Biol Med 141:1014-1016, 1972). This action occurs within the hypothalamus, as complete surgical isolation does not alter it (Blake CA, Norman RL and Sawyer CH, Localization of the inhibitory actions of estrogen and nicotine on release of luteinizing hormone in rats. Neuroendocrinology 16:22-35, 1974) and it is not exerted at the pituitary, which is still fully responsive to exogenous LHRH. (Blake CA, Norman RL and Sawyer CH, Effects of hypothalamic deafferentation

and ovarian steroids on pituitary responsiveness to LH-RH in female rats. In Gual and Rosemberg, eds, Hypothalamic hypophysiotropic hormones. Excerpta Medica, Amsterdam, 1973, pp. 33-38). Although nicotinic effects alone are inhibitory, the data indicate that the net effect of acetylcholinesterase inhibition or acetylcholine administration is to stimulate gonadotropin secretion in the short term.

Summary of the Invention

The present invention provides a method of treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis such as failure of ovulation, some cases of unexplained infertility, luteal phase defect, hypogonadotrophic hypogonadism, aesthenozoospermia, oligozoospermia, delayed onset of puberty and cryptorchidism.

Detailed Description of the Invention

Suitable acetylcholinesterase inhibitors for the present invention include those that have a central effect and have a medium to long duration of action (such as from 1 to 100 hours, typically from 1.5 to 72 hours). Suitable acetylcholinesterase inhibitors are those that will pass easily through the blood-brain barrier. Suitable compounds for this purpose include donepezil, rivastigmine, galantamine, lycoramine and the analogs of galantamine and lycoramine. The most suitable compounds for this purpose are galanthamine, lycoramine and their analogs wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group or a trialkylsilyloxy group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

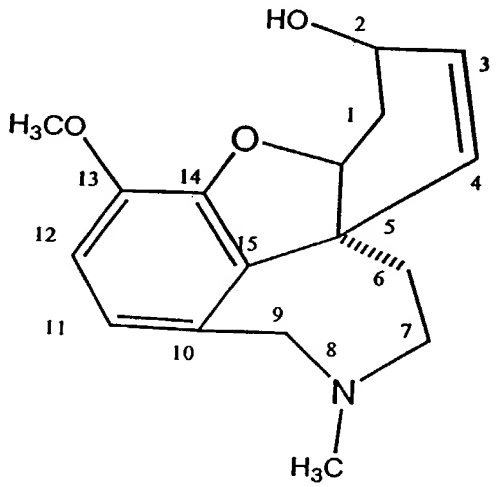
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.

One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

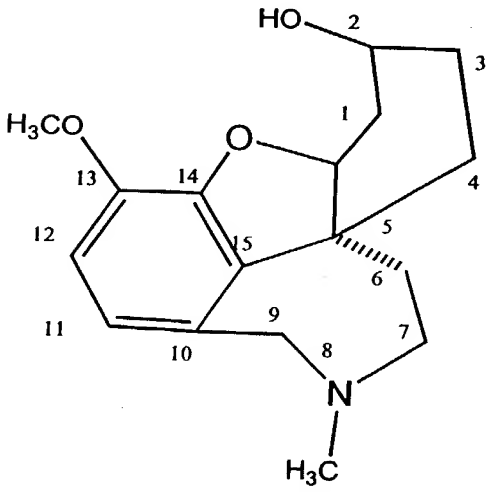
When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl. When reference is made to alkyl groups, where the context permits, the term also includes groups which are or contain cycloalkyl groups including adamantyl. Aryl groups are typically phenyl or naphthyl but may include heteroatyl such as morpholino.

Galanthamine and lycoramine have the following formulae:

Galanthamine



Lycoramine



Suitable analogs are described for example in International Patent Publication WO 88/08708 and an article by Bores and Kosley in Drugs of the Future 21: 621-631 (1996). Other useful pharmacologic agents for such

preparations include rivastigmine, and other pharmacologic agents with half lives of 1-11 hours.

Particularly useful analogs of galanthamine and lycoramine that are of use in the present invention include analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group, for example an alkanoyloxy of from one to seven carbon atoms or benzoyl group, or where the methoxy group is replaced by a mono or dialkyl carbamate or a mono or dialkyl carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 8 carbon atoms or wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Other useful analogs include compounds wherein, independently of whether or not the methoxy group has been replaced, the hydroxy group is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an acyloxy group, for example an alkanoyloxy group, typically of from 1 to 7 carbon atoms, a benzoyloxy or substituted benzoyloxy group wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups, a carbonate group or a carbamate group which may be a mono or dialkyl or an aryl carbamate or carbonate wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

GnRH and various longer acting agonists are used in a wide variety of clinical situations. They may be used to stimulate or suppress the HPG axis. They may be used alone, or in combination with gonadotropic preparations, hormones, or hormone antagonists. Short-term (or pulsatile) administration of GnRH stimulates gonadotropin secretion, while continuous administration or the use of long acting analogs for more than approximately two weeks desensitizes the

gonadotropes and decreases gonadotropin secretion. This "medical castration" has numerous applications. (Ascoli M and Segaloff DL, Adenohypophyseal hormones and their hypothalamic releasing factors, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, McGraw-Hill, New York, 1996, pp 1363-1382)

The peptides used to influence the reproductive axis must be given by injection, infusion or intranasally. LH and FSH preparations, including HCG and HMG, are given by injection. The subject of the present invention is the use of moderate or long-acting, orally available, centrally active cholinergic agents to stimulate gonadotropin secretion, alone or in combination with gonadotropins, GnRH, GnRH analogs or other hormonal preparations.

Oral cholinergic agents may, in suitable patients, substitute for parenteral medications such as testosterone preparations or gonadotropins. The use of these agents could avoid the need for injections, subcutaneous or intravenous infusion pumps, and the inconvenience and risk of infection. Manipulation of the HPG axis for ovulation induction at the level of the hypothalamus is more physiological than GnRH and gonadotropins. It may be expected to reduce the incidence of ovarian hyperstimulation syndrome and multiple gestations, because normal feedback inhibitory mechanisms can operate at the level of the pituitary gland and the hypothalamus, just as the use of GnRH, acting on the pituitary gland, decreased the incidence of these complications from that of gonadotropin therapy, which acts directly on the ovaries. (Blacker CM, Ovulation stimulation and induction. Endo Metab Clin N Am 21(1):57-83, 1992).

The preferred agents for use in the present invention are rivastigmine and galantamine. Donepezil may be used in certain situations. These are acetyl-cholinesterase inhibitors which are well absorbed orally and partition preferentially to brain.

Rivastigmine has a plasma half life of 1-2 hours and is administered in doses of 0.5 to 10 mg two to six times a day, with a maximum daily dose of 18 mg. (Product Monograph: Exelon, Novartis Pharma AG, Basel, Switzerland, April 1998) Galantamine has a plasma half-life of 5 hours and is administered in doses of 1-20 mg two to four times a day with a maximum dose of 60 mg a day. (Westra P,

et al Pharmacokinetics of galantamine (a long-acting anticholinesterase drug) in anaesthetized patients. Br J Anaesth 58:1303-1307, 1986; Mihailova D, et al Pharmacokinetics of galantamine hydrobromide after single subcutaneous and oral dosage in humans. Pharmacology 39:50-58, 1989). Donepezil is given in doses of 1-15 mg once daily. (Rogers SL, et al A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Neurology 50:136-145, 1998) Doses for children may be proportionately reduced, and controlled-release dosage forms may override multiple dose schedules.

Common side effects include nausea and vomiting, anorexia, dizziness, fatigue, acsthenia. They are lessened by slow buildup of dose, and decrease with continued administration. Donepezil produces a higher frequency of muscle cramps than the shorter acting drugs, and insomnia, which they do not produce.

Cholinergic agents may exacerbate depression. Cholinergic agents exert vagotonic effects on the heart, and thus may exacerbate the sick sinus syndrome or bradycardia and may cause bronchoconstriction, particularly in patients with asthma and chronic obstructive pulmonary disease, may increase gastrointestinal motility or acid secretion, may theoretically increase bladder motility, may cause seizures or worsen Parkinsonian symptoms, or the symptoms of organophosphate anticholinesterase poisoning. There are insufficient data on the teratogenicity to rule out possible fetal malformations, and data on the safe use of these compounds in children are needed as well.

Ovulation-Inducing Protocols

Many patients with hypogonadotropic amenorrhea or hypothalamic dysfunction who are properly evaluated and followed and are deemed candidates for infusion pump treatment with GnRH may respond to the oral administration of acetylcholinesterase inhibitors. Protocols vary considerably among centers with the use of stimulatory agents guided by rises in plasma hormone measurements and ultrasound determinations of ovarian follicle size. The evaluation and monitoring used for GnRH administration would be used with acetylcholinesterase inhibitor ovulation induction. In the protocol employed by Blacker, for example, (Blacker CM, Ovulation stimulation and induction, Endo Metab Clin N Am 21(1):57-83,

1992) therapy is begun at the beginning of the follicular phase with the intermediate-acting agents, galantamine at 2-5 mg tid or rivastigmine at 1-2 mg tid, or appropriate delayed-release dosage form of either compound. If a normal follicular response as determined by transvaginal ultrasound or serum estradiol levels is not obtained, the dose may be increased to a maximum of galantamine, 15-20 mg tid, or rivastigmine, 4-6 mg tid, as tolerated. If the response is excessive at any point, dosages must be reduced to prevent ovarian hyperstimulation or multiple gestation. In unusual cases, the doses may be increased to galantamine, 30-35 mg tid, or rivastigmine, 8 mg tid. The small decrease in plasma hormone levels immediately preceding ovulation may be reproduced by decreasing or withholding medication for a short period. Luteal support may be provided by continuing the galantamine or rivastigmine for approximately two weeks, preferably at lower doses. Alternatively, luteal support may be provided, as in Blacker's description, with GnRH infusion, HCG injections, or progesterone administration. Determination of a suitable dose may be accomplished by means known to those skilled in the art. It is, however, likely that the dose will vary between individuals and that it will only be established after several menstrual cycles.

Additional GnRH protocols have been described by Miller MM, Hoffman DI, Ovulation induction, in KL Becker, ed, Principles and Practice of Endocrinology and Metabolism JB Lippincott, Philadelphia, 1995, pp 900-909; Ascoli M and Segaloff DL, Adenohypophyseal hormones and their hypothalamic releasing factors, in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edition, McGraw-Hill, New York, 1996, pp 1363-1382; Fauser and Van Heusden, Endo Rev 18(1):71-106, 1997.

Superovulation in the Treatment of Unexplained Infertility

Cholinergic agents stimulate gonadotropin secretion in short-term studies of experimental animals and are of use in promoting the development of additional follicles during normal menstrual cycles in infertility cases. Studies with clomiphene or HMG injection suggest an increase in observed pregnancy rates. (Deaton JL, Gibson M, Nakajima ST et al, A randomized controlled trial of clomiphene citrate and intrauterine insemination versus well-timed intercourse in couples with unexplained infertility or surgically corrected endometriosis, Fertil

Steril 54:1083, 1990; Collins JA, Superovulation in the treatment of unexplained infertility. Semin Reprod Endocrinol 8:165, 1990). A protocol similar to ovulation induction may be followed, with treatment continuing into the luteal phase if required due to luteal phase insufficiency, or standard luteal phase therapies may be used.

Luteal Phase Defect

Luteal phase dysfunction may be treated by acetylcholinesterase inhibitors of the present invention, using endometrial biopsies and serum progesterone concentrations to assess outcome. Treatment is begun at 2-5 mg galantamine bid or tid, or 1-2 mg rivastigmine tid, and increased every few days in small increments until the desired result is obtained. It will take several cycles to establish the correct dose. Correction of the luteal phase dysfunction may require initiating treatment during the follicular phase. (Rebar RW, Disorders of menstruation, ovulation and sexual response, in KL Becker, ed, Principles and Practice of Endocrinology and Metabolism, JB Lippincott, Philadelphia, 1995, pp 880-899)

Hypogonadotropic Hypogonadism

Cholinesterase inhibitors of the present invention are of use for the stimulation of endogenous GnRH in patients who are potentially responsive such as women with functional hypothalamic amenorrhea, male acquired idiopathic hypogonadotropic hypogonadism, some cases of Kallman's syndrome or other hypothalamic dysfunction who may not have complete absence of GnRH cells. Initial doses of 2-5 mg of galantamine bid or tid or 1-2 mg of rivastigmine could be raised by 4 mg of galantamine per day once a week, or 1-2 mg of rivastigmine once a day per week to a daily dose of 15-75 mg of galantamine or 8-18 mg of rivastigmine, with the final dose taken not later than late afternoon, to avoid continuous stimulation and subsequent downregulation. Alternatively, donepezil beginning at 5 mg/day, increasing to 10 mg/day after four weeks may be administered. Some patients may tolerate up to 15 mg/day. The lowest effective doses should be used.

The outcome measurements could, depending on the clinical objective and gender, include FSH or LH measurements, menstrual function, estradiol,

progesterone or testosterone measurements, or sperm counts. Gonadotropin secretion should be monitored at intervals to ensure that stimulation has not been superseded by suppression after long-term treatment.

Induction of Puberty

The treatment protocol is essentially the same as for hypogonadotropic hypogonadism. Patients whose gonads and pituitary glands are responsive to GnRH, after priming, may have hypothalamic function sufficient to respond to cholinergic therapy. Given that the expected treatment with GnRH would involve several years of use of a portable infusion pump, a trial of oral cholinergic therapy may be reasonable to assess its potential. Using dosing regimens described above for hypogonadotropic hypogonadism, and allowing for a two-month period to comfortably reach an optimal dose with minimal induction of side effects, followed by four months of therapy, a six-month trial would be recommended to assess the potential for efficacy in an individual patient. The optimal dose will be individualized as with GnRH. Outcome measures may include hormone or gonadotropin measurements, testicular volume, growth velocity and development of secondary sexual characteristics. Gonadotropin secretion should be monitored at intervals to ensure that stimulation has not been superseded by suppression after long-term treatment.

Oligozoospermia and/or Aesthenozoospermia

Infertile males with normal or abnormal gonadotropins and low sperm counts or abnormal sperm characteristics have been treated with GnRH preparations with improvements. (Aulitzky W, Frick J, Hadziselimovic F, Pulsatile LHRH therapy in patients with oligozoospermia and disturbed LH pulsatility. Int J Androl 12(4):265-72, 1989; Matsumiya K, Kitamura M, Kishikawa H, Kondoh N, Fujiwara Y, Okuyama A, A prospective comparative trial of a gonadotropin-releasing hormone analogue with clomiphene citrate for the treatment of oligoaesthenozoospermia. Int J Urol 5(4):361-3, 1998). The same treatment regimen as proposed for hypogonadotropic hypogonadism is used here. A minimum of three months therapy is necessary to evaluate effects on sperm.

Cryptorchidism

Some cases of undescended testes respond to treatment with LHRH

and/or HCG. (Lala R, Matarazzo P, Chiabotto P, Gennari F, Cortese MG, Canavese F, DeSanctis C, Early hormonal and surgical treatment of cryptorchidism. J Urol 157(5):1898-1901, 1997; Fedder J and Boesen M, Effect of a combined GnRH/hCG therapy in boys with undescended testicles: evaluated in relation to testicular localization within the first week after birth. Arch Androl 40(3)181-186, 1998). A trial of treatment of boys with cryptorchidism with cholinesterase inhibitors would follow the protocol proposed for hypogonadotrophic hypogonadism, with weight-based dosage adjustments.

Dosages set out above have been for galanthamine or rivastigmine. However, dosages for other suitable agents can be determined by standard techniques such as those set out for example in Chapter 6 (by Benjamin Calesnick) of Drill's Pharmacology in Medicine (Fourth Edition Joseph R DiPalma ed, McGraw-Hill 1971 or in Chapter 6 (by B. E. Rodda et al) of Biopharmaceutical Statistics for Drug Development (ed. Karl E. Peace, Marcel Dekker Inc, 1988).

What I claim is:

1. A method of treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis which comprises administering to a patient suffering from such a condition an effective amount of an acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours.

2. A method as claimed in claim1 wherein said duration of action is from 1.5 to 72 hours.

3 A method as claimed in claim 1 orclaim 2 wherein said condition is failure of ovulation.

4. A method as claimed in claim 1 or claim 2 wherein said defect is an unexplained infertility.

5. A method as claimed in claim 1 or claim 2 wherein said condition is a luteal phase defect.

6 A method as claimed in claim 1 or claim 2 whererin said defect is hypogonadotrophic hypogonadism

7. A method as claimed in claim 1 or claim 2 wherein said condition is aesthenozoospermia.

8. A method as claimed in claim 1 or claim 2 wherein said condition is oligozoospermia

9. A method as claimed in claim 1 or claim 2 wherein said condition is delayed onset of puberty.

10. A method as claimed in claim 1 or claim 2 wherein said condition is cryptorchidism.

11. A method as claimed in claim 1 or claim 2 wherein said acetyl cholinesterase inhibitor is selected from the group consisting of donepezil, rivastigmine, galantamine, lycoramine and the analogs of galantamine and lycoramine.

12. A method as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

13. A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

14 A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

15. A method of treatment as claimed in claim 14 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

16. A method of treatment as claimed in claim 15 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

17. A method of treatment as claimed in claim 16 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

18 A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

19 A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

20 A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyloxy group of from one

to seven carbon atoms.

21. A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is galanthamine.

22. A method of treatment as claimed in claim 1 or claim 2 wherein said acetylcholinesterase inhibitor is rivastigmine.

23. A medicine for treatment treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis which comprises an effective amount of an acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours.

24 Use of an acetylcholinesterase inhibitor having a central effect and a duration of action of from 1 to 100 hours for preparation of a medicament for treatment of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis.

ABSTRACT

Acetylcholinesterase inhibitors are of use for treating a variety of conditions that can benefit from stimulation of the hypothalamic-pituitary-gonadal axis such as failure of ovulation, some cases of unexplained infertility, luteal phase defect, hypogonadotrophic hypogonadism, aesthenozoospermia, oligozoospermia, delayed onset of puberty and cryptorchidism. Suitable acetylcholinesterase inhibitors include donepizil, rivastigmine galanthamine, lycoramine and analogs thereof.

#7

Practitioner's Docket No. U 013729-7 ***PATENT***

Optional Customer No. Bar Code

00140

PATENT TRADEMARK OFFICE

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[ ] original.
[ ] design.

NOTE: *With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1.312 (Amendments after allowance). M.P.E.P. Section 714.16, 7th Ed.*

[ ] supplemental.

NOTE: *If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item; check appropriate one of last three items.*

[x] national stage of PCT.

NOTE: *If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P.*

NOTE: *See 37 C.F.R. Section 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application.*

[ ] divisional.
[ ] continuation.

NOTE: *Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. Section 1.53(b) (application filing requirements-nonprovisional application).*

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: *If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.*

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

USE OF ACETYLCHOLINESTERASE INHIBITORS ON THE MODULATION OF THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE: "The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60).

(b) [ ] was filed on _____, [ ] as Application No. _____
[ ] and was amended on _____ (if applicable).

NOTE: Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 C.F.R. Section 1.67.

NOTE: "The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R. Section 1.63:

(A) application number (consisting of the series code and the serial number, e.g., 08/123,456);
(B) serial number and filing date;
(C) attorney docket number which was on the specification as filed;
(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or
(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g., 08/123,456), or serial number and filing date. Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.

M.P.E.P. Section 601.01(a), 7th ed.

(c) [x] was described and claimed in PCT International Application No. US99/28972 filed on DECEMBER 8, 1999 and as amended under PCT Article 19 on _____ *(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent if the foreign application is referred to in the oath or declaration as required by Section 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. Section 119(b) must be filed in the case of an interference (Section 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in Section 1.17(i). If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner; or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C.F.R. Section 1.55(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [ ] such applications have been filed as follows.

NOTE: Where item (c) is entered above and the International Application which designated the U.S. itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, **MONTH**, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER	**FILING DATE**
60 / 111,913	December 11, 1998
/	
/	

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. SECTION 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY*, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

_____

_____

_____

NOTE: If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. Section 120.

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179

JOHN RICHARDS, 31053

(10) RICHARD J. STREIT, 25765

PETER D. GALLOWAY, ~~27885~~

RICHARD P. BERG, 28145

JULIAN H. COHEN, 20302

WILLIAM R. EVANS 25858

JANET I. CORD, 33778

CLIFFORD J. MASS, 30086

CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

[ ] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

[ ] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE: "Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4)." Section 601.03, M.P.E.P., 7th Ed

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)

JOHN RICHARDS
(212) 708-1915

(complete the following if applicable)

Since this filing is a [ ] continuation [ ] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document.

NOTE: Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C.F.R. Section 1.63(a)(3).

NOTE: Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor. 62 Fed. Reg. 53,131, 53,142, October 10, 1997,

Full name of sole or first inventor

1-CD

Bonnie _____ _____ **DAVIS**
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature (x) Bonnie L

Date (x) August 2, 2002 **Country of Citizenship** USA

Residence 160 COLD SPRING, SYOSSET, N.Y. 11791 USA NY

Post Office Address SAME AS ABOVE

Full name of second joint inventor, if any

_____ _____ _____
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of third joint inventor, if any

_____ _____ _____
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* _____

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. Section 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. Section 1.47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[x] This declaration ends with this page.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: BONNIE DAVIS

Serial No.: PCT/US99/28972 Group No.:

Filed: 8 DEC. 1999 Examiner:

For: USE OF ACETYLCHOLINESTERASE INHIBITORS ....

Attorney Docket No.: U 013729-7

Assistant Commissioner for Patents
Washington, D.C. 20231

WRITTEN ASSERTION OF SMALL ENTITY STATUS

This is written assertion on the basis of:

☒ personal knowledge;
☐ applicant's letter of _____;
☐ applicant's agent's letter of _____; or
☐ other _____

by a practitioner (not necessarily of record) that the above application is entitled to small entity status and, therefore, fees.

Respectfully submitted,

JOHN RICHARDS
C/O LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, N.Y. 10023

CERTIFICATION UNDER 37 C.F.R. 1.8(a) and 1.10*
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

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☐ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.
37 C.F.R. 1.8(a)

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☐ transmitted by facsimile to the Patent and Trademark Office.

Date: November 27, 2001

Signature

JENNIFER RASHKIN
(*type or print name of person certifying*)

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"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

SCANNED, # #24

United States Patent & Trademark Office

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Application deficiencies found during scanning:

☒ Page(s) 12 of Specification was ~~were~~ not present for scanning.
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